Non-invasive positive pressure ventilation for the treatment of severe stable chronic obstructive pulmonary disease: a prospective, multicentre, randomised, controlled clinical trial

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Summary

Background Evidence is weak for the ability of long-term non-invasive positive pressure ventilation (NPPV) to improve survival in patients with stable hypercapnic chronic obstructive pulmonary disease (COPD). Previous prospective studies did not target a reduction in hypercapnia when adjusting ventilator settings. This study investigated the effect of long-term NPPV, targeted to markedly reduce hypercapnia, on survival in patients with advanced, stable hypercapnic COPD.

Methods This investigator-initiated, prospective, multicentre, randomised, controlled clinical trial enrolled patients with stable GOLD stage IV COPD and a partial carbon dioxide pressure ($PaCO_2$) of 7 kPa (51·9 mm Hg) or higher and pH higher than 7·35. NPPV was targeted to reduce baseline $PaCO_2$ by at least 20% or to achieve $PaCO_2$ values lower than 6·5 kPa (48·1 mm Hg). Patients were randomly assigned (in a 1:1 ratio) via a computer-generated randomisation sequence with a block size of four, to continue optimised standard treatment (control group) or to receive additional NPPV for at least 12 months (intervention group). The primary outcome was 1-year all-cause mortality. Analysis was by intention to treat. The intervention was unblinded, but outcome assessment was blinded to treatment assignment. This study is registered with ClinicalTrials.gov, number NCT00710541.

Findings Patients were recruited from 36 respiratory units in Germany and Austria, starting on Oct 29, 2004, and terminated with a record of the vital status on July 31, 2011. 195 patients were randomly assigned to the NPPV group (n=102) or to the control group (n=93). All patients from the control group and the NPPV group were included in the primary analysis. 1-year mortality was 12% (12 of 102 patients) in the intervention group and 33% (31 of 93 patients) in the control group; hazard ratio 0·24 (95% CI 0·11–0·49; p=0·0004). 14 (14%) patients reported facial skin rash, which could be managed by changing the type of the mask. No other intervention-related adverse events were reported.

Interpretation The addition of long-term NPPV to standard treatment improves survival of patients with hypercapnic, stable COPD when NPPV is targeted to greatly reduce hypercapnia.

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Introduction

Advanced-stage chronic obstructive pulmonary disease (COPD) is characterised by severe bronchial obstruction, pulmonary hyperinflation, and chronic ventilatory failure. Ventilatory failure is thought to be a result of respiratory muscle insufficiency[1] and alterations in central ventilatory control.[2] The consequences of ventilatory failure are chronic hypercapnia and (compensated) respiratory acidosis. Previous studies suggest that chronic hypercapnic respiratory failure is inversely associated with overall prognosis.[3]

In patients with chronic hypercapnic respiratory failure, long-term non-invasive positive pressure ventilation (NPPV) has been shown to improve important physiological variables such as blood gases and lung hyperinflation.[4] Results from clinical studies showed improvements in exercise capacity (6-min walk distance,[5] exercise-related dyspnoea,[6] pulmonary cachexia,[7] and sleep quality[8]). Furthermore, disease-specific aspects of health-related quality of life (HRQL) reportedly improve in patients with COPD following long-term NPPV.[9] Additionally, NPPV treatment might be associated with fewer hospital admissions and lower overall treatment costs.[10]

Despite these positive indicators, large randomised trials have failed to document survival benefits when NPPV was added to long-term oxygen treatment compared with long-term oxygen treatment alone.[11,12] Results from the most recent randomised trial showed a small survival benefit, but this benefit was at the cost of worsened HRQL.[13] However, NPPV in these studies was done using quite low inspiratory pressures and therefore did not improve hypercapnia. The best results with long-term NPPV have been noted in studies using more intensive forms of NPPV, with higher inspiratory pressures and high backup frequencies that improved or even normalised hypercapnia.[14] The effects of such an approach to NPPV on patient survival has yet to be determined.

This study investigated the effect of long-term NPPV, targeted to markedly reduce hypercapnia, on outcomes in patients with advanced COPD with chronic

hypercapnic respiratory failure receiving optimised standard treatment.[15]

Methods

Study design and patients

This was an investigator-initiated, multicentre, prospective, randomised, controlled clinical trial using a PROBE design.[16] Patients were recruited from 36 respiratory units in Germany and Austria, starting on Oct 29, 2004, and terminated with a record of the vital status on July 31, 2011.

Patients with clinically stable, hypercapnic GOLD stage IV COPD, aged 18 years or older, were eligible for this study if they had a baseline arterial carbon dioxide pressure ($PaCO_2$) of 7 kPa (51·9 mm Hg) or higher and a pH higher than 7·35, measured after at least 1 h rest in a sitting position. Patients were judged as clinically stable if they had no acute exacerbation (defined as an increase in or new onset of more than one respiratory symptom [cough, sputum production, sputum purulence, wheezing, or dyspnoea] lasting 2 days or more and requiring any change of pharmacological treatment) during the 4-week run-in period before randomisation.

Patients were ineligible if they had abnormalities of the thorax or the lung other than COPD, obesity with a body-mass index (BMI) ≥35 kg/m², or other conditions resulting in hypercapnia. Additional exclusion criteria were previously-initiated NPPV, malignant co-morbidities, severe heart failure (New York Heart Association stage IV), unstable angina, and severe arrhythmias. We did not include patients in impaired general condition that could preclude regular follow-up visits (appendix; study protocol).

Primary care physicians were encouraged to refer successive patients with chronic hypercapnic COPD to one of the study centres. No further screening procedure was applied. We did not include a highly selected group of patients to maintain the generalisability of the results. Each of the participating clinical centres was advised to record the screening of their patients with COPD (eligible, not eligible, randomised) in a screening log. All patients were being treated according to the national COPD and long-term oxygen treatment guidelines.[17,18]

The study protocol was approved by the local ethics committees of all participating institutions. The study was designed and performed according to the Declaration of Helsinki 2004. Patients gave written informed consent before participating in the trial.

Randomisation and masking

After a 4-week run-in period patients were admitted to hospital and randomly assigned (in a 1:1 ratio) to either the non-invasive positive pressure ventilation group or the control group. Randomisation was stratified according to study site. For each of the 36 study sites, an independent statistician produced computer-generated block randomisation lists with a block size of four patients. After inclusion of a patient, the peripheral investigators called a 24 h hotline at the coordinating centre, where an independent study coordinator registered the patient's baseline data and then disclosed the group allocation for this patient. We applied the PROBE Design[16] because NPPV cannot be blinded, and an effective sham measure is not available. Staff members who performed NPPV were aware of the treatment assignment of every participant. Outcome assessors were unaware of treatment assignment throughout the study.

Procedures

Patients in the control group received optimised COPD therapy without NPPV. NPPV was allowed temporarily in the case of an acute exacerbation with an increase in $PaCO_2$ of more than 10 kPa (74 mm Hg; appendix). In the intervention group, patients received optimised COPD therapy plus NPPV. They were advised to use NPPV for at least 6 h per day, preferably during sleep, but usage during daytime was also accepted.

They were followed-up for at least 1 year. In the first year, regular follow-up visits were scheduled at 14 days, and 3, 6, 9, and 12 months after randomisation. All patients from both groups were admitted to hospital for the follow-up visits to ensure optimised medical treatment and optimised NPPV. Additionally, all patients were contacted by telephone every 4 weeks to monitor health status, detect problems with technical devices, and ensure adherence to therapy.

NPPV was done according to national recommendations.[19] Patients were treated with ventilators marketed not earlier than 2004 from manufacturers ResMed (Martinsried, Germany), Weinmann (Hamburg, Germany), or Tyco Healthcare (Neuburg, Germany), all set in pressure support ventilation mode. Ventilation with high backup rates to achieve controlled ventilation was preferred, but assisted ventilation was also acceptable if patients did not tolerate high backup rates. NPPV was targeted to reduce baseline $PaCO_2$ by 20% or more, or achieve $PaCO_2$ values lower than 6·5 kPa (48·1 mm Hg). We assessed treatment compliance using the internal time meters on the ventilator. Face masks or nasal masks were used according to the clinical judgment of the investigators. Specialised nurses trained patients at all study centres; they thoroughly practised familiarisation with the interface and the ventilator after randomisation, and did re-assessments of mask fitting, ventilator settings, and technical control of the equipment at all follow-up visits. Additionally, health-care providers were available within 24 h for customer calls at patients' homes in case of technical problems with the mask, ventilator, or long-term oxygen treatment. In patients with long-term oxygen treatment, supplemental oxygen was inserted into the ventilator or into the circuit during ventilation.

Each study centre regularly assessed survival status of study patients. For patients lost to clinical follow-up, we retrieved survival status from the national population register. We did all blood gas measurements from arterialised capillary ear lobe blood during spontaneous

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See **Online** for appendix

For the **study protocol** see http://mh-hannover.de/fileadmin/kliniken/pneumologie/Pneumologie_Homepage/PDFs/NIV_in_COPD_15122003.pdf

breathing, at least 1 h after patients had switched from NPPV to spontaneous breathing. Patients under long-term oxygen treatment received oxygen via nasal cannula at a flow rate as previously prescribed. We assessed lung function and 6-min walk distance as previously specified.[20–22] Staff who took these measurements were masked to treatment assignment and not involved in the study. Long-term oxygen treatment patients received oxygen during the 6-min walk test.

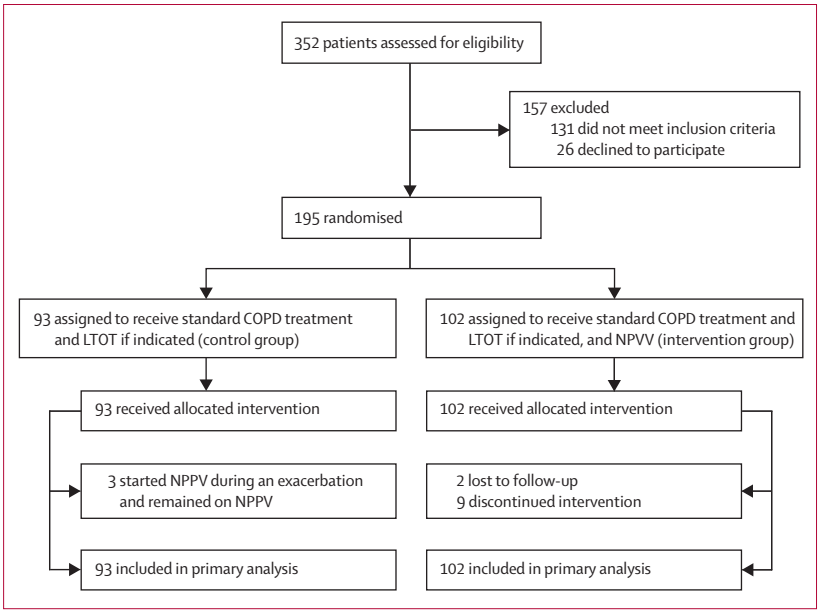

Figure 1: **Trial profile**
COPD=chronic obstructive pulmonary disease. LTOT=long-term oxygen therapy. NPPV=non-invasive positive pressure ventilation.

	Control group (n=93)	Non-invasive positive pressure ventilation group (n=102)
Age, years	64·4 (8·0)	62·2 (8·6)
Male, n (%)	56 (60%)	65 (64%)
Body-mass index, kg/m²	24·5 (5·8)	24·8 (5·8)
FVC, % predicted	53·3% (13·8)	50·4% (13·3)
FEV_1, % predicted	27·5% (8·9)	26% (11·0)
FEV_1/FVC, %	41·2% (11·4)	40·4% (11·5)
Residual volume/total lung capacity, %	72·7% (8·9)	73·0% (8·5)
pH	7·39 (0·05)	7·39 (0·04)
$PaCO_2$, kPa	7·7 (0·7)	7·8 (0·8)
PaO_2, kPa*	8·7 (1·9)	8·6 (2·1)
SaO_2, %*	90·8% (5·9)	90·3% (6·2)
HCO_3^-, mmol/L	33·9 (4·1)	34·3 (4·0)
Base excess, mmol/L	8·0 (3·9)	7·8 (3·8)
6-min walk distance, m	249·6 (145·3)	226·7 (121·2)
Long-term oxygen treatment, n (%)	60 (65%)	67 (66%)

Data are mean (SD), unless otherwise stated. FVC=forced vital capacity. FEV_1=forced expiratory volume in 1 s. $PaCO_2$=arterial carbon dioxide pressure. PaO_2=arterial oxygen pressure. SaO_2=arterial oxygen saturation. HCO_3^-=bicarbonate. *In patients with long-term oxygen treatment, oxygen was applied via nasal cannula at the previously prescribed flow rate.

Table 1: **Baseline demographic and clinical characteristics of patients**

We assessed HRQL using validated German versions of the Short Form-36 (SF-36)[23] and St George's Respiratory Questionnaire (SGRQ).[24] We used the Severe Respiratory Insufficiency (SRI) questionnaire[25] as a tool to specifically assess HRQL in patients receiving long-term home mechanical ventilation.

The study protocol provided that adverse events were recorded during all visits and during the telephone calls.

Statistical analysis

1-year mortality for patients fulfilling the inclusion criteria was previously estimated as 20–22%.[26] Extending COPD treatment with NPPV was expected to reduce the relative mortality risk by 30%[4] (α=5%; β=20%, power=80%). We calculated a sample size of 150 patients per group. Baseline characteristics are presented for the intention-to-treat population, and according to treatment assignment. Continuous variables are reported as mean (SD) and categorical variables are presented as frequencies and percentages.

The primary outcome, one-year patient survival, was assessed in the intention-to-treat population using the Kaplan-Meier approach and the log rank test. Hazard rate reduction was assessed using a Cox proportional hazards model with NPPV treatment as a time-dependent covariate (on-treatment analysis). We assessed proportional hazards assumption by visual inspection of log-log plots and tested using the rank of analysis time as the time-scaling function. We analysed long-term survival to end of observation in the same way as the primary endpoint analysis. We used linear mixed models to analyse the effect of NPPV on changes from baseline to follow-up of secondary endpoints ($PaCO_2$, arterial oxygen pressure [PaO_2], arterial oxygen saturation [SaO_2], pH, bicarbonate [HCO_3^-], forced vital capacity [FVC], forced expiratory volume in one second [FEV_1], residual volume/total lung capacity, 6-min walk distance) and HRQL summary measures (SF-36, SGRQ, SRI). Except for pH and HRQL, we studied relative changes for better comparison of effects in secondary endpoints; for this purpose, we calculated CIs for logarithms and then transformed them to the percent scale to receive appropriate asymmetric CIs larger than 0. We adjusted all models for baseline age, and sex. To take the cluster structure of the data into account, we included random intercepts for patient and study site. For repeated measurements, we applied a first order autoregressive structure. We used a logistic regression for non-responder analysis (questionnaires not returned or not assessable). We deemed a two-tailed p value lower than 0·05 to be significant. We did all analyses using SAS Version 9.4 (SAS Institute).

Role of the funding source

None of the sponsors had any role in the design and conduct of the study, the collection, management, analysis and interpretation of the data, the preparation, review, or approval of the report, or the decision to

submit the manuscript for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

195 (55%) of 352 patients who were referred to a study centre fulfilled all criteria and could be randomly assigned to treatment (figure 1). In August 2010, a national guideline on NPPV treatment was published including recommendations for COPD patients.[27] This guideline provided more liberal application criteria for NPPV establishment than those used in this study, and this therefore prevented enrolment of patients into the study and resulted in premature cessation of patient recruitment. Baseline characteristics were similar in both treatment groups (table 1). One patient in the control group was recognised immediately after randomisation to have an acute COPD exacerbation. This patient stayed in the group and in the analysis. During the 1-year study period, two patients from the NPPV group were lost to follow-up, both at day 14.

At study entry, patients were admitted to hospital for a mean of 2·5 (0·2) days for the control group and 5·6 (SD 1·1) days for the intervention group. For follow-up visits at 14 days, 3 months, 6 months, 9 months, and 12 months, patients were electively admitted to hospital for 2·0 (0·1) days in the control group and 3·1 (0·9) days in the intervention group.

Emergency hospital admissions were rare (table 2). Three patients (3%) in the control group were treated with acute NPPV during an acute exacerbation of COPD, and all three continued on NPPV for the rest of the observation period. In the intervention group, nine patients (9%) discontinued NPPV treatment (appendix). The reasons were mask intolerance in five patients, and patients' impression of uselessness of NPPV in four. Long-term oxygen treatment was newly initiated for 12 patients in the control group and 11 patients in the intervention group during the 1-year observation period, with oxygen flow rates of 1–3 L/min.

Data for ventilatory pressures and backup frequencies were available in 85 patients (83%) in the intervention group. The mean inspiratory pressure was 21·6 cmH_2O (4·7) and the mean expiratory pressure 4·8 cmH_2O (1·6). The mean backup frequency was 16·1±3·6 (range 2–24) min^{-1}. 70 patients (69%) had backup rates of 14 min^{-1} or higher. At least one measure of exact ventilator usage was available in 122 3-months follow-up periods in a subset of 48 patients (47%), of whom 65% (52·5% of periods) exceeded the prescribed usage time of more than 6 h per day. Usage time was less than 3 h in 18·8% of patients (23·8% of periods). Mean NPPV usage was 5·9 h per day (3·1).

For the primary endpoint, 31 (33%) of 93 patients in the control group, and 12 (12%) of 102 patients in the intervention group died within 1 year after randomisation (log rank p=0·0004; hazard ratio (HR) 0·24, 95% CI 0·11–0·49; figure 2). Proportional hazards assumption was not violated (p=0·16, appendix). After 1 year, the survival benefit in the intervention group was maintained (log-rank p=0·0023; appendix, HR not constant over time, p=0·0305).

Improvements from baseline to follow-up in $PaCO_2$, pH, SaO_2, HCO_3^-, and FEV_1 reached significance in patients receiving NPPV compared with controls. No significant between-group differences were noted for changes in PaO_2, FVC, 6-min walk distance and residual volume/total lung capacity (table 3). Results for 6-min walk distance did not reach the predefined significance level, but the suggested[28] minimal clinically important increase in 6-min walk distance of 54 m was reached by 45 (44%) patients in the intervention group versus 23 (25%) control patients. Table 4 shows the observed means of $PaCO_2$ for all visits.

We did HRQL assessments in selected study centres (24 of 36) at least once during follow-up in 111 patients (59 in the intervention group, 52 patients in the control group). The analysis of patients answering or not answering the questionnaires to assess HRQL showed a significant gender effect (67·6% response in women, 52·1% response in men, p=0·0344) and no effect of group, age or BMI, or their two-way interactions. 80 patients (44 in the intervention group, 36 in the control group) with

	3 months	6 months	9 months	12 months
Overall	0·8 (3·5)	2·1 (5·7)	0·9 (4·0)	2·6 (8·6)
Non-invasive positive pressure ventilation group	0·2 (1·1)	1·4 (4·7)	1·3 (4·9)	2·2 (10·2)
Control group	1·5 (4·9)	3·0 (6·9)	0·4 (1·9)	3·1 (5·4)

Values are mean (SD).

Table 2: **Emergency hospital admissions per patient by follow-up period and treatment group**

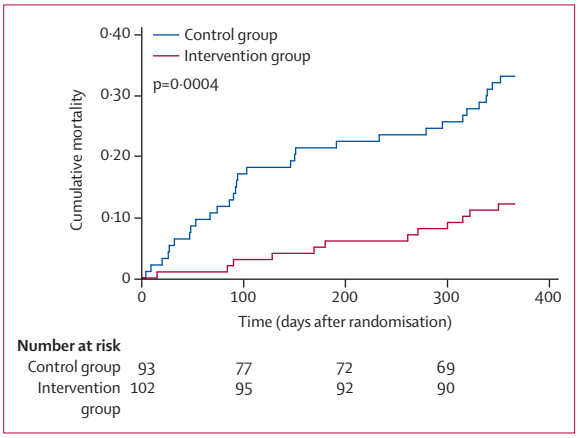

Figure 2: **Kaplan-Meier estimate of cumulative all-cause mortality during the first year after randomisation (primary outcome)**
The p value results from a log-rank test of the between-group difference.

	Control group		Non-invasive positive pressure ventilation group		Difference	p value
	One-year change from baseline, adjusted for baseline, age and sex (95% confidence interval)	Number of patients who contributed to estimation (%)	One-year change from baseline, adjusted for baseline, age and sex (95% confidence interval)	Number of patients who contributed to estimation (%)		
$PaCO_2$	−2·4% (−3·7% to −1·1%)	69/83 (83%)	−7·4% (−8·6% to −6·2%)	79/89 (89%)	−5·1% (−6·8% to −3·4%)	<0·0001
PaO_2	1·4% (−0·3% to 3·2%)	69/83 (83%)	2·2% (0·6% to 3·8%)	79/89 (89%)	0·8% (−1·6% to 3·1%)	0·53
SaO_2	0·5% (0·1% to 1·0%)	63/76 (83%)	1·1% (0·7% to 1·5%)	71/79 (90%)	0·6% (0·0% to 1·2%)	0·0405
HCO_3-	−2·1% (−3·2% to −0·9%)	53/65 (82%)	−5·0% (−6·0% to −4·0%)	63/71 (89%)	−3·0% (−4·6% to −1·5%)	0·00018
FVC	0·1% (−1·9% to 2·2%)	66/78 (85%)	−0·2% (−2·1% to 1·8%)	72/87 (83%)	−0·3% (−3·1% to 2·5%)	0·83
FEV_1	-0·8% (−2·6% to 1·0%)	66/78 (85%)	2·0% (0·2% to 3·8%)	71/86(83%)	2·8% (0·2% to 5·4%)	0·034
Residual volume/total lung capacity	0·2% (−0·7% to 1·2%)	61/73 (84%)	0·1% (−0·8% to 1·0%)	69/80 (86%)	−0·2% (−1·4% to 1·1%)	0·81
6-min walk distance	0·0% (−5·5% to 5·8%)	60/71 (85%)	7·6% (1·9% to 13·6%)	65/79 (82%)	7·6% (−0·5% to 16·2%)	0·07
pH*	0·006 (−0·002 to 0·013)	68/83 (82%)	0·020 (0·013 to 0·028)	79/89 (89%)	0·015 (0·025 to 0·004)	0·0056

$PaCO_2$=arterial carbon dioxide pressure. PaO_2=arterial oxygen pressure. SaO_2=arterial oxygen saturation. HCO_3^-=bicarbonate. FVC=forced vital capacity. FEV_1=forced expiratory volume in 1 s. Percent changes, 95% CIs, and p values were calculated using logscale repeated measurement mixed models with patients and centres as random effects and baseline, age, and sex as fixed effects. *Changes from baseline for pH are absolute values rather than percent change because pH is measured on a log scale.

***Table 3*: Secondary endpoints (change from baseline after 1 year)**

	Baseline	14 days	3 months	6 months	9 months	12 months
All patients	7·9 (0·8)	7·0 (1·1)	7·0 (1·1)	6·7 (1·0)	6·8 (0·9)	6·9 (1·1)
Control group	7·9 (0·7)	7·5 (1·1)	7·4 (0·9)	7·1 (1·0)	7·3 (0·8)	7·4 (1·2)
Non-invasive positive pressure ventilation group	8·0 (0·8)	6·6 (0·9)	6·6 (1·1)	6·4 (0·9)	6·4 (0·9)	6·5 (0·9)

Values are mean (SD).

***Table 4:* Arterial carbon dioxide pressure (kPa) during the 1-year study**

follow-up HRQL assessments were included into the mixed model analysis. Changes in SF-36 score did not differ significantly between treatment groups, apart from the General Health Perception subscale, which improved to a greater extent (8·6 points, 95% CI 1·8–13·3) in the intervention group compared with the control group (p=0·0133; figure 3A, appendix). The SGRQ summary score improved more (6·2 points, 95 % CI 0·7–11·8) in the intervention group (p=0·0289; figure 3B). The minimal clinically important decrease of 4 points in the SGRQ[29] was reached by 26·4% of patients in the NPPV group versus 28·9% in the control group. Changes in the SRI summary scale score were in favour of the NPPV group (difference of 5·6 points, 95 % CI 0·1–11·1; p=0·0445; figure 3C). 14 (14%) patients reported skin rash at the facial skin, which could be managed by changing the type of the mask. No other adverse effects were reported that could be attributable to the intervention. Since minor skin lesions can often happen during NPPV, we did not judge this as a relevant adverse event.

Discussion

The main finding of this study is the positive effect of long-term NPPV on overall survival in patients with hypercapnic, chronic, stable COPD. This survival benefit became evident over 1 year of treatment and seemed to persist thereafter without further increase, although a formal proof of long-term results for more than 1 year was beyond the scope of this study. Additionally, continuous 1-year NPPV treatment was associated with significant improvements in $PaCO_2$, pH, bicarbonate, FEV_1, and HRQL.

The findings of the current study are in contrast to the results of previous randomised trials showing that NPPV did not improve long-term survival.[11,12] The main difference between these trials and our study is the technique used to apply NPPV. In previous studies, NPPV did not significantly reduce hypercapnia. Also, in the most recent randomised trial (n=144),[13] NPPV did not improve blood gases. Thus, even though a significant survival benefit was seen in an adjusted Cox model, the unadjusted model showed no significant improvement in survival with NPPV. In the current study, the mean inspiratory pressure was 22 cmH_2O, and many patients received high back-up rates or even controlled ventilation. The present findings support the concept that unloading of the ventilatory muscles with higher NPPV doses (pressure support and usage times) can improve alveolar ventilation and thereby reduce chronic hypercapnia.

To our knowledge, this trial brings for the first time strong supporting evidence that NPPV targeted to greatly reduce $PaCO_2$ (decrease baseline $PaCO_2$ by ≥20% or achieve $PaCO_2$ <6·5 kPa [48·1 mm Hg]) improves long-term survival (panel). An additional important finding was that HRQL significantly improved with NPPV treatment. This finding could be shown by both generic and highly specific HRQL assessment methods. By contrast, HRQL predominantly remained stable in the previous randomised trial[13] and even deteriorated in two of the eight subscales of the SF-36. However, only generic aspects of HRQL (SF-36) were investigated, even though the assessment of HRQL following a specific treatment intervention has been shown to require the application of disease-specific assessment methods.[30] Additionally, low-pressure ventilation, as discussed above, might also have

contributed to the finding that HRQL was not improved. However, previous findings suggest that SF-36 scores can improve when $PaCO_2$ is reduced in patients with COPD after NPPV.[9]

Other strengths of the present trial include the methods to minimise bias (blinded and centralised randomisation, PROBE design, and intention-to-treat analysis). Furthermore, the present study assessed the largest COPD cohort studied prospectively for a survival benefit of NPPV. The trial aimed to maintain routine practice in both groups as much as possible. NPPV was not done with predefined pressure settings. Instead, ventilator settings were individually tailored according to body constitution, airway obstruction, and compliance of the lungs and the thorax to achieve a maximum of CO_2 reduction in all patients. Backup breathing frequencies were slowly increased in the initiation phase to reach controlled ventilation. Most patients tolerated frequencies between 14 and 24 breaths per min, which was similar to the strategy of Dreher and colleagues[14] who described best treatment effects by the application of controlled ventilation.

By targeting the prespecified reduction in $PaCO_2$, patients in the NPPV group received a range of ventilator pressure settings and minimum backup frequencies. Ventilator settings were adjusted during all follow-up visits. We cannot exclude the possibility that these settings became inefficient during the 3-month periods between the study visits, especially in patients with inspiratory pressure settings below the average or low backup frequencies. Influencing factors might be patients' adherence to other treatment components (pharmacotherapy, physiotherapy) and progression of COPD. The study thus presents the net effect on mortality that can be expected under real life conditions. The mortality rates in the current control group were higher than those reported in the trial of McEvoy and colleagues,[13] even though our control patients received intense medical attention. This difference might be explained by different inclusion criteria. McEvoy and colleagues[13] included patients with mild hypercapnia ($PaCO_2$ > 6·2 kPa *vs* 7·0 kPa in our study), and baseline hypercapnia in McEvoy's patients was less severe (7·3 kPa in the control group and 7·1 kPa in the intervention group) versus 7·7 kPa and 7·8 kPa in both groups in our study.

During the follow-up visits, average fluctuation of the SGRQ was plus or minus two points (figure 3B). Interestingly, the minimum clinically important improvement of four points in the SGRQ was achieved by a number of control group patients. The authors have no clear explanation for this phenomenon, which was even larger than in other clinical trials (TORCH,[31] UPLIFT[32]).

There are several limitations to our study. Similar to a previous study,[13] patients with chronic stable COPD eligible for these trials are rarely treated in hospital, and therefore recruitment took 6 years. However, no relevant changes in ventilator technology and COPD treatment guidelines took place over this period. Patients in the control group were treated with acute NPPV only when they had hypercapnia with a $PaCO_2$ of 10 kPa or higher, regardless of pH. At the time of protocol development, the investigators expected severe patients with hypercapnic COPD to have high baseline bicarbonate levels, resulting from chronic renal compensation. Bicarbonate levels and pH fluctuations are dependent

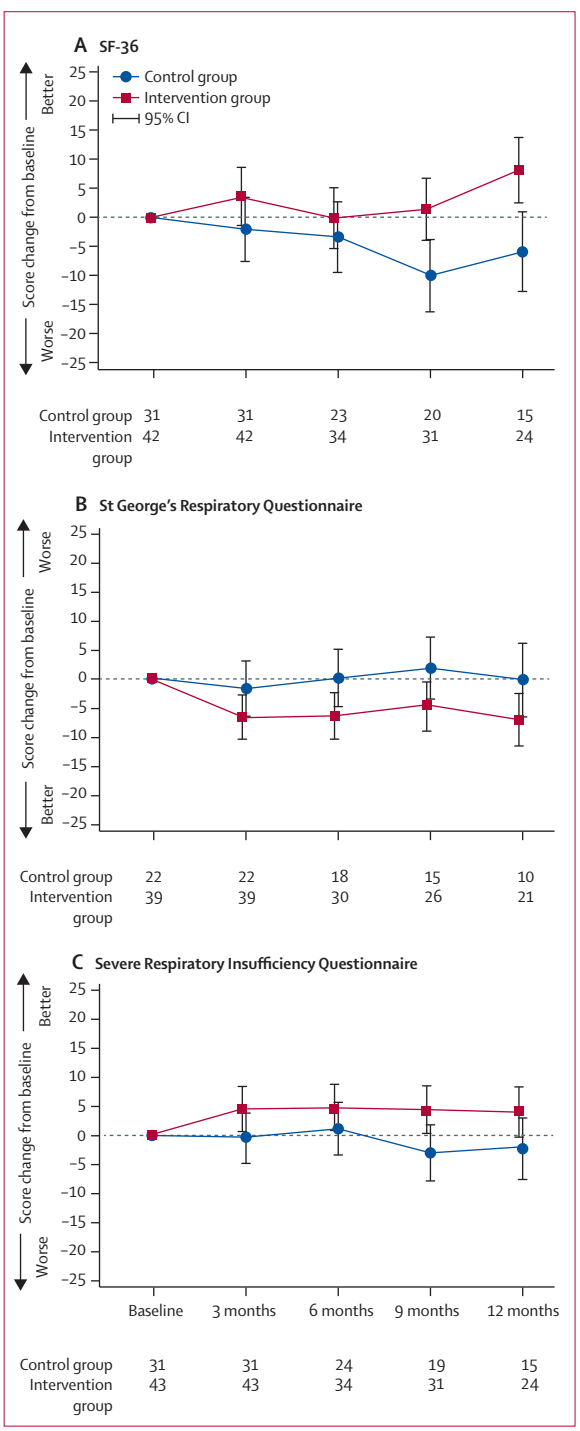

***Figure 3*: Changes from baseline in secondary quality of life outcomes (HRQL in patients with severe, stable COPD with or without additional long-term NPPV treatment)**
HRQL=health-related quality of life. SF-36=short form 36 health survey. (A) HRQL assessed by the generic questionnaire SF-36;[23] significantly greater improvements in the general health perception subscale were noted in the NPPV group (p=0·0133; appendix). (B) disease-specific HRQL assessed using the St George's Respiratory Questionnaire;[24] lower values indicate better HRQL; the summary score improved by 5·8 points more in the intervention group (p=0·0289). (C) The Severe Respiratory Insufficiency Questionnaire[25] specifically assesses HRQL in patients with long-term home mechanical ventilation; higher values indicate better HRQL; the HRQL improved by 5·6 points more in the intervention group (p=0·0445).

Panel: **Research in context**

Systematic review

We searched PubMed for reports in any language published before June 30, 2004, using the search terms "COPD" AND "non-invasive ventilation" AND "clinical trial". We identified four clinical trials.[8,10–12] In all studies, low ventilatory pressures were applied, which did not result in sufficient improvement in alveolar ventilation. Two studies assessed overall outcome, and both did not document an effect on survival in patients with severe, stable hypercapnic COPD treated with NPPV compared with those on long-term oxygen treatment. During the course of the present study, another multicentre, randomised, controlled clinical trial was published, which showed a small survival benefit by the addition of NPPV treatment at the cost of worsened health-related quality of life.[13] No notable safety concerns were raised in these trials.

Interpretation

After follow-up of 12 months, long-term treatment with NPPV with increased ventilatory pressures that reduced hypercapnia was associated with significant and sustained improvements in overall mortality, quality of life, and exercise capacity in patients with severe, stable hypercapnic COPD. Thus, long-term NPPV seems to offer important benefits in this patient group, but the treatment success might be dependent on effective ventilatory strategies.

on renal function, and the investigators wanted to exclude any renal influences. Therefore, $PaCO_2$ was selected as the variable on which to base the decision to initiate acute NPPV treatment in the control group. Patients with acidosis in the control group with a $PaCO_2$ lower than 10 kPa might have been treated late with acute NPPV. This aspect had no major effect on the survival in the control group, since only two control group patients died in one of the study centres. All the other control patients reached the primary endpoint at local hospitals that applied their own standards, or died outside hospital.

Treatment allocation and intervention could not be masked because sham NPPV for 1 year in the control group was not deemed to be appropriate. Secondary endpoint analysis might be biased because of the differential mortality in the two groups, but we assume the effect to be small due to baseline adjustment and use of relative changes instead of absolute changes. HRQL data were incomplete because only selected study centres were prepared to provide three questionnaires per visit to their patients and, especially in the late phase of the study, many questionnaires were not returned. Thus, the representativeness of HRQL data might be small. The protocol provided for hospital admissions every 3 months. These scheduled hospital admissions might interfere with necessary hospital admissions due to the natural course of the disease or for acute exacerbations. Therefore, it was not possible to interpret signals relating to frequency of exacerbations and use of primary health-care services.

Sample size did not reach the intended target, but the mortality effect was larger than anticipated. Although the study has less power for secondary endpoints than planned, it is still deemed to be sufficient because endpoints measured on metric scales usually require smaller sample sizes than mortality trials. The study power was not calculated to assess long-term outcomes after the 12-month observation period. Similar to the findings of McEvoy and colleagues,[13] our findings in the appendix suggest a continuing survival benefit in the NPPV group. Although in our study the numbers of patients at risk were even higher for 3 years or more, both studies do not have sufficient power to interpret long-term survival. Potential adverse effects of NPPV were not systematically assessed in the current study. Increased inspiratory pressures have been reportedly associated with a lower cardiac output.[33] However, this trial was purely physiological, covering short periods of daytime NPPV only, and exclusively used non-invasive techniques (echocardiography) for cardiac output measurements. Therefore, there is still no clear evidence for negative cardiac effects of long-term NPPV. Nevertheless, further research is needed to elucidate the effect of long-term NPPV using higher pressures on haemodynamics. Finally, only a few centres were able to provide measurements of mouth occlusion pressures according to the international standards,[34] and could offer sufficient capacity in their sleep laboratories. Obligatory sleep studies had to be omitted from the study protocol so as not to endanger the conduct of the study that included short time frames for follow-up appointments (±10 days), despite the fact that most patient used NPPV during sleep.

In conclusion, our study provides evidence that the addition of NPPV targeted to greatly reduce hypercapnia to standard treatment improves overall survival, exercise capacity, and HRQL over 1 year in patients with chronic hypercapnic COPD compared with guideline-oriented COPD treatment without NPPV.

Contributors

TK had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. TK, TW, CPC, DK, and GL-G came up with the study concept and design. TK, JG, SH, OK, BSchö, BSchu, and CPC participated in the data acquisition. AD and KW did the data analysis and interpretation. TK, WW, and SN drafted the report, and all authors then critically reviewed it for important intellectual content. AD and KW did the technical analysis. TW and OK obtained the study funding while TK and AD provided administrative, technical, or material support. The Trial Steering Committee consisted of TW, CPC, GL-G, DK, and TK.

Declaration of interests

TK has received grants and lecture fees from Deutsche Lungenstiftung, Resmed, Tyco, Weinmann, and Heinen und Löwenstein. WW has received open research grants and speaking fees from Weinmann, Vivisol, Breas Medical, Respironics; and he is an advisory board member at Maquet and Respironics. JG has received consultancy fees from Weinmann and Philips-Respironics; and fees for lectures from Philips-Respironics, Hill-Rom, Heinen und Löwenstein, Weinmann, Resmed,

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